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Note

Synthesis of 3,4-dihydro-3,3-dimethyl-1(2H)-acridinone

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The acridinone derivative 3,4-dihydro-3,3-dimethyl-1(2H)-acridinone (**4**) has been prepared in a two step fashion and the molecular structure confirmed by X-ray diffraction. Compound **4** crystallizes in the space group $P2_1/n$ with a = 6.022(2), b = 21.111(2), c = 9.604(2) Å, β = 99.97(2)°, and Z = 4. The single crystal analysis showed the acridinone tricyclic ring is virtually planar except in the gem-dimethyl position of C(3) which presented a half-chair conformation.

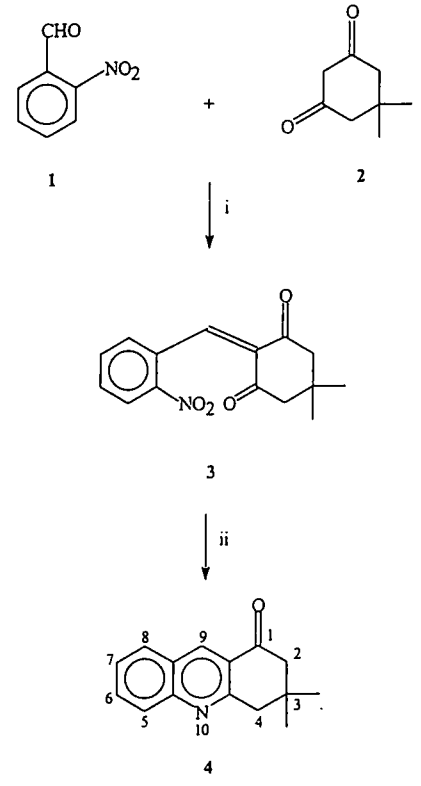
KEY WORDS: Acridinone, alzheimer, dimedone.

Introduction

Acridinone derivatives have been proposed as potential antimalarial,[2] anti-AIDS,[3] antitumor,[4] and particularly in the case of some aminotetrahydroacridines derivatives such as Tacrine, Velnacrine, and Suronacrine, considered as promising anti-Alzheimer drugs.[5] In the search for more effective anti-Alzheimer drugs we have prepared 3,4-dihydro-3,3-dimethyl-1(2H)-acridinone **4** in a two-step reaction and its single crystal structure elucidated by X-ray diffraction analysis.

Experimental

The intermediate **3** was prepared by refluxing equimolar amounts of 2-nitrobenzaldehyde **1**, dimedone **2**, and KOH in ethanol over 3 h. Sodium dithionite promoted reduction of the resulting nitro derivative **3** and further cyclization furnished acridinone **4** (Scheme 1). This reaction was carried out refluxing **3** with 12 eq. of sodium dithionite in ethanol over 5 h. Also the reduction step of **3** was carried out under a hydrogen atmosphere with Pd/C as a catalyst at 60 psi of pressure to give compound **4** in similar yields (15%). Preparation of a closely related acridinone derivative of **4** has been previously described using a secondary amine, dimedone, formaldehyde and perchloric acid to give the corresponding water soluble quaternary salts of the N-alquil-substituted acridinones.[6]



Scheme 1. Reactions and conditions: (i) KOH/EtOH-H_2O, reflux, 3 h. (ii) $Na_2S_2O_4$/EtOH-H_2O, reflux, 5 h.

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Table 1. Summary of crystal and intensity collection data for compound **4**

Compound	$C_{15}H_{15}NO$
Color/shape	colorless/irregular
Formula weight	225.3
Space group	$P2_1/n$
Temp., °C	20
Cell constants[a]	
a(Å)	6.022(2)
b(Å)	21.111(2)
c(Å)	9.604(2)
β(°)	99.97(2)
V(Å^3)	1202.5(5)
Z	4
ρ calc (mgcm^{-3})	1.244
μcalc, mm^{-1}	0.611
Diffractometer/scan	Siemens P4-PC/$2\theta/\theta$
Radiation	Cu$K\alpha$(λ = 1.54178 Å)
Crystal dimensions (mm)	0.34 × 0.36 × 0.24
Unique reflections	1613
2θ range, deg.	10 to 110
hkl range	±6, ±22, ±10
Reflections observed [$F > 3\sigma(F)$][b]	1419
Solution and Refinement	SHELXTL PLUS (PC version)[7]
Solution	Direct methods
Refinement method	Full-matrix least-squares
Number of parameters refinement	155
Weighting scheme	$[\sigma^2(F) + 0.0008F^2]^{-1}$
Goodness-of-fit	1.28
$R = \Sigma \|\|Fo\| - \|Fc\|\|/\Sigma\|Fo\|$	4.76%
Rw	5.22%
Largest feature final diff. map	0.19 e/Å^3

[a] Least-squares refinement of 38 centered reflections ($8.36 < 2\theta < 39.855$).
[b] Corrections: Lorentz-polarization.

Results and discussion

The spectroscopic characterization of compound **4** was performed by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The IR spectrum exhibits a characteristic absorption band at 1688 cm^{-1} for the ketone group present in the aliphatic ring. The mass spectrum gave a molecular ion at m/z 225 in agreement with the formula weight of compound **4** and a base peak at m/z 169. The proton resonance displayed signals at δ 1.2 for methyls, δ 2.7, 3.2 for methylene groups and at δ 7.5–8.0 for the aromatic protons. The ^{13}C NMR (DEPT) showed one signal at δ 28 ppm for two methyl groups, two signals at δ 47 and δ 52 for the methylene groups of the fused aliphatic ring and five aromatic carbons at δ 126–136. The final elucidation of the molecular structure was achieved by X-ray diffraction analysis of a single crystal (Tables 1–4). The single crystal analysis showed the acridinone tricyclic ring is virtually planar except in the

Table 2. Bond lengths (Å) for compound **4**

O(1)−C(1)	1.213(2)	C(1)−C(2)	1.488(3)
C(1)−C(11)	1.497(3)	C(2)−C(3)	1.535(3)
C(3)−C(4)	1.530(3)	C(3)−C(15)	1.521(4)
C(3)−C(16)	1.525(4)	C(4)−C(12)	1.502(3)
C(5)−C(6)	1.363(3)	C(5)−C(13)	1.416(3)
C(6)−C(7)	1.407(3)	C(7)−C(8)	1.357(3)
C(8)−C(14)	1.414(3)	C(9)−C(11)	1.367(3)
C(9)−C(14)	1.404(3)	N(10)−C(12)	1.324(2)
N(10)−C(13)	1.371(3)	C(11)−C(12)	1.423(3)
C(13)−C(14)	1.413(3)		

Table 3. Bond angles (°) for compound **4**

O(1)−C(1)−C(2)	122.2(2)	O(1)−C(1)−C(11)	121.0(2)
C(2)−C(1)−C(11)	116.8(2)	C(1)−C(2)−C(3)	114.1(2)
C(2)−C(3)−C(4)	107.8(2)	C(2)−C(3)−C(15)	110.0(2)
C(4)−C(3)−C(15)	109.8(2)	C(2)−C(3)−C(16)	110.3(2)
C(4)−C(3)−C(16)	110.0(2)	C(15)−C(3)−C(16)	108.9(2)
C(3)−C(4)−C(12)	113.9(2)	C(6)−C(5)−C(13)	119.3(2)
C(5)−C(6)−C(7)	121.6(2)	C(6)−C(7)−C(8)	120.1(2)
C(7)−C(8)−C(14)	120.3(2)	C(11)−C(9)−C(14)	119.9(2)
C(12)−N(10)−C(13)	118.3(2)	C(1)−C(11)−C(9)	120.5(2)
C(1)−C(11)−C(12)	120.1(2)	C(9)−C(11)−C(12)	119.3(2)
C(4)−C(12)−N(10)	117.0(2)	C(4)−C(12)−C(11)	120.7(2)
N(10)−C(12)−C(11)	122.3(2)	C(5)−C(13)−N(10)	118.0(2)
C(5)−C(13)−C(14)	119.3(2)	N(10)−C(13)−C(14)	122.7(2)
C(8)−C(14)−C(9)	123.2(2)	C(8)−C(14)−C(13)	119.4(2)
C(9)−C(14)−C(13)	117.3(2)		

Table 4. Atomic coordinates (×10^4) and temperature factors (Å^2 × 10^3) for **4**

	x	y	z	U(eq)[a]
O(1)	−5398(3)	5910(1)	1152(2)	70(1)
C(1)	−3899(3)	6000(1)	2152(2)	48(1)
C(2)	−3957(3)	6535(1)	3154(3)	53(1)
C(3)	−1641(3)	6828(1)	3707(2)	47(1)
C(4)	−100(3)	6302(1)	4417(2)	48(1)
C(5)	3879(3)	4462(1)	3255(3)	51(1)
C(6)	4018(4)	3924(1)	2488(3)	58(1)
C(7)	2234(4)	3729(1)	1430(3)	62(1)
C(8)	322(4)	4080(1)	1145(3)	57(1)
C(9)	−1795(3)	5038(1)	1641(2)	48(1)
N(10)	1806(3)	5372(1)	3769(2)	44(1)
C(11)	−1888(3)	5572(1)	2431(2)	43(1)
C(12)	−36(3)	5724(1)	3512(2)	42(1)
C(13)	1896(3)	4834(1)	2980(2)	43(1)
C(14)	114(3)	4645(1)	1903(2)	46(1)
C(15)	−1865(5)	7346(1)	4775(3)	70(1)
C(16)	−653(4)	7114(1)	2490(3)	60(1)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

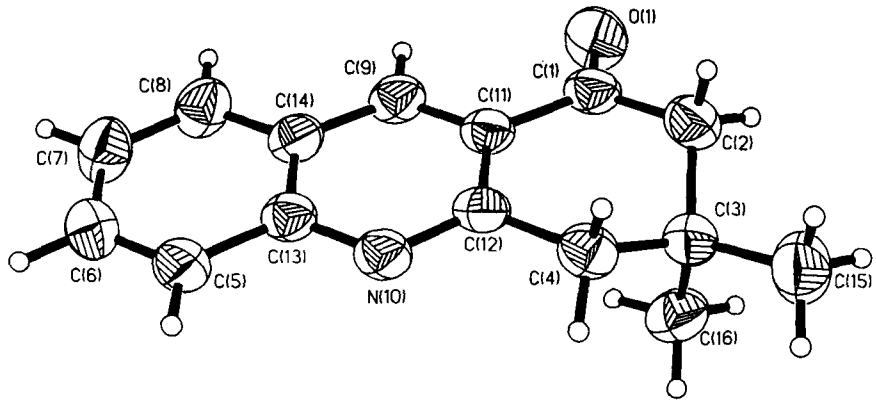

Fig. 1. Crystal structure of compound **4**.

gemdimethyl position of C(3) which presented a half-chair conformation (Fig. 1). To our knowledge this is the first report of X-ray diffraction analysis of an acridinone derivative and only for the anti-Alzheimer drugs Tacrine, Velnacrine, and Suronacrine have powder diffraction analyses been reported.[8] The described structures were in good agreement with the structure of **4**; however, bond lengths and angles could not be compared since these data were not provided in reference 8.

Acknowledgments

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References

1. Contribution No. 1254 from Instituto de Quimica, UNAM.
2. Kesten, S.J.; Degnan, M.J.; Hung, J.; McNamara, D.J.; Ortwine, D.F.; Uhlendorf, S.E.; Werbel, L.M. *J. Med. Chem.* **1992,** *35,* 3429.
3. Shutske, G.M. *Chem. Abstr.* **1993,** *118,* 45771.
4. Cholody, W.M.; Konopa, J.; Antonini, I.; and Martelli, S. *J. Heterocyclic Chem.* **1991,** *28,* 209.
5. Shutske, G.M.; Pierrat, F.A.; Kapples, K.J.; Cornfeldt, M.L.; Szewczak, M.R.; Huger, F.P.; Bores, G.M.; Haroutunian V. and Davis, K.L. *J. Med. Chem.* **1989,** *32,* 1805.
6. Kornilov, M.Y.; Turov, A.V.; Mel'nik, M.V.; Gutsulyak, B.M. *Zh. Org. Khim.* **1979,** *15,* 2226.
7. Sheldrick, G.M. SHELXTL-PLUS PC *User's Manual*; Siemens Analytical X-ray Instruments: Madison, WI., 1990.
8. Bandoli, G.; Nicolini, M.; Ongaro, A. *Powder Diffr.* **1991,** *6,* 196.